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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/913,955	Applicant(s) CRINE ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *7-12,14-19,22-32 and 35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,13,20,21,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-40 are pending.

Applicant's election with traverse of Group I, claims 1-6, 13, 20-21 drawn in part to a PHEX enzyme and variants thereof, in Paper No. 9, filed on 10/2/2002 is acknowledged.

Applicant's submission of a new sequence listing in paper and electronic form, in Paper No. 13, filed on 1/30/2003 is acknowledged.

Applicant's traverse is on the ground(s) that the Examiner has not identify any classes and subclasses, therefore it has not been possible to ascertain whether searching two or more groups would impose an undue burden on the Office. Applicants request submission of classes/subclasses for each of the groups in response to their communication. Furthermore, Applicants argue that if the restriction is maintained, Applicants would have to submit 10 divisional applications for the non-elected groups, thereby giving rise to significant expense.

Upon further consideration, Group I and Group VIII (claims 33-34), which is drawn to a method of use of the polypeptide of Group I (i.e. method of obtaining PHEX ligands with PHEX), will be examined in the instant application in accordance with 37 CFR 1.475(2). Applicant's arguments have been fully considered but are not deemed persuasive to overcome the restriction requirement in regard to Groups I-VII, IX-XI. The Examiner acknowledges the significant costs associated with filing 10 applications, however this is an issue which is beyond the Examiner's control. In regard to classes/subclasses not being provided in the previous Office Action, it is noted that the instant application was filed under 35 USC 371 as the national stage of PCT/CA00/00201. As such, the restriction requirement was applied based on 35 USC 121

and 372. As indicated in previous Office Action Paper No. 8, mailed on 7/2/2002, claims 1-40 were found to lack unity of invention under PCT Rule 13.1. Therefore in accordance with 37 CFR 1.499, the claims were restricted. While it is acknowledged that classes/subclasses are provided for each group when the application is filed under 35 USC 111, this is not required when filed under 35 USC 371. However, upon Applicant's request, the following classes/subclasses would have to be search at a minimum in each group, as follows:

Group I, claim(s) 1-6, 13, 20-21, drawn in part to a PHEX enzyme and variants thereof, class 435, subclass 212.

Group II, claim(s) 7-12, 20, drawn in part to DNA, vectors, host cells and expression of a PHEX enzyme, class 435, subclass 320.1, 252.3, 69.1

Group III, claim(s) 14-18, 22-25, drawn to an antibody against a PHEX enzyme, class 530, subclass 387.1.

Group IV, claim(s) 19, drawn to a hybridoma cell producing an antibody against a PHEX enzyme, class 435, subclass 326.

Group V, claim(s) 26, drawn to a method for detecting the presence of PHEX, class 435, subclass 4.

Group VI, claim(s) 27, 29, drawn to a device for purifying PHEX, class 435, subclass 287.2.

Group VII, claim(s) 28, 30-32 drawn to a device for screening PHEX ligands, class 435, subclass 287.1.

Group VIII, claim(s) 33-34, drawn to a method for obtaining a PHEX ligand, class 436, subclass 501.

Group IX, claim(s) 35-38, drawn to methods for determining the activity of PHEX and a PHEX substrate, class 435, subclass 18.

Group X, claim(s) 39, drawn to a method for screening for inhibitors of PHEX, class 435, subclass 7.1.

Group XI, claim(s) 40, drawn to a kit for use in a method for determining the activity of PHEX and a PHEX substrate, class 424, subclass 94.63.

While the Examiner is not arguing that the restriction requirement is proper due to the undue burden of searching all the claimed inventions in one application, in response to Applicant's arguments in regard to the burden of searching the entire application as filed, it is noted that searching the entire application would impose an undue burden on the Office as evidenced by the large number of classes/subclasses indicated above, and also taking into consideration the fact that these are the minimum classes/subclasses which would be required for search.

For the reasons set forth in previous Office Action Paper No. 8, mailed on 7/2/2002, unity of invention is lacking. As such, the requirement is deemed proper and therefore is made FINAL.

Claims 7-12, 14-19, 22-32, 35-40 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It is noted that some of the elected claims are still partially drawn to non-elected inventions. Examination of such claims will be restricted to the subject matter elected, which in the instant case is a PHEX enzyme and variants thereof. Applicants are requested to amend the claims accordingly in response to this Office Action.

Applicants are advised that if in response to this Office Action, amendments are introduced which would require searching more than one sequence, the claims may be subjected to an additional restriction requirement.

Specification

1. The specification is objected for not complying with sequence rules. Several drawings disclose sequences however neither the Brief Description of the Drawings nor the drawings indicate specific sequence identifiers for such sequences. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification. See particularly 37 CFR 1.821(d). Appropriate correction is required.

2. The specification is objected to due to the recitation of "glutamic acid residue in position 582" in page 29, line 4, since one cannot determine which sequence is being referred to in the absence of a sequence identifier or a statement defining said sequence. It is noted that according to Figure 2, position 582 corresponds to a phenylalanine residue. For examination purposes, it will be assumed that the term refers to position 581 of the sequence disclosed in Figure 2. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to CANADA 2262056 filed on 02/24/1999.

4. This application is the national stage of PCT/CA00/00201 filed on 02/24/2000.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on 12/4/2001 and 3/6/2003 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

6. The drawings have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

7. Claim 20 is objected to because the instant claim is partially drawn to a non-elected invention, i.e. nucleic acid. For examination purposes, the claim will be interpreted as being directed to the elected subject matter only, i.e. PHEX enzyme. Appropriate correction is required.

8. Claims 1-6, 33, 34 are objected to due to the recitation of "PHEX". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-6, 13, 20-21, 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1-2 (claims 3-6, 20-21, 33-34 dependent thereon) are indefinite in the recitation of "purified PHEX enzyme....and variants thereof, comprising a PHEX ectodomain or catalytic part thereof..." as it is unclear if the term is further limiting the variants or if it applies to both: the purified PHEX and its variants. If the term is intended to limit both, it is suggested that the claims be amended to recite "wherein said ..enzyme and said variants comprise...". For examination purposes, it will be assumed that the term refers to the purified PHEX and its variants. Correction is required.

12. Claim 2 is indefinite in the recitation of "modified so as to confer solubility to ....when expressed in a eukaryotic host, wherein said host is not a human being" as it is unclear if the term "eukaryotic host wherein said host is not a human being" excludes humans and human cells, or if only human beings are excluded but not human cells. For example, as written, it is unclear if the protein of claim 2 expressed in HeLa cells or 293 cells, which are cultivated in vitro, would be within the scope of the claim. For examination purposes, it will be assumed that the term excludes humans and human cells. Correction is required.

13. Claims 4-6 are indefinite in the recitation of "enzyme having the glutamic acid residue at position 581" as it is unclear absent a statement indicating the specific sequence to which the position belongs. It is suggested that if said specific sequence has been disclosed in the sequence listing, the claim be amended to include the specific sequence identifier (i.e. SEQ ID NO: #)

which corresponds to the position recited. For examination purposes, no patentable weight will be given to the term. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-6, 13, 20-21, 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. Claims 1, 13, 20-21 are drawn to a genus of soluble PHEX enzymes or variants thereof which comprise a PHEX ectodomain or a catalytic part of said ectodomain. Claim 2 adds the limitation that the PHEX enzyme comprises a signal peptide/transmembrane region modified in any way to confer solubility. Claims 3-6 are drawn to a genus of mutants of a PHEX enzyme which are inactive but can bind PHEX ligands. Claims 33-34 are drawn to a method of obtaining PHEX ligands by contacting test molecules with the genus of enzymes of claim 1. While the specification discloses the preparation of a soluble form of the PHEX enzyme as disclosed in Figure 2 (sequence), and a mutated form of the enzyme of Figure 2 wherein position 581 of said enzyme is substituted with a valine residue, the specification fails to disclose the structure of other PHEX enzymes, active and inactive, as encompassed by the claims from other sources,

including other human or murine PHEX enzymes. No disclosure of the critical structural elements required in a polypeptide to display PHEX function has been provided either. Furthermore, the specification fails to disclose which are the residues in any PHEX enzyme which would render such enzyme inactive if substituted or deleted, and still retain the ability to bind any PHEX ligand. In addition, while the specification discloses the use of a signal peptide fused in frame with the ectodomain of human PHEX and substitutions of selected amino acids in the signal peptide/transmembrane region (page 18, last paragraph), there is no disclosure of other modifications in the signal peptide/transmembrane region as encompassed by the claims.

While one could argue that the claimed invention is adequately described in view of what is being disclosed in the specification and in view of the fact that at least one human and one murine PHEX enzyme were known in the art at the time the invention was made, it is noted that an adequate description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. In the instant case, no structural features are recited and the specification does not provide the structural features necessary for members of the genus to be selected. The specification only discloses a single species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera required to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed. Applicants are referred to the revised guidelines concerning compliance with the written

description requirement of 35 USC 112, first paragraph, published in the Official Gazette and also available at the USPTO website.

17. Claims 1-6, 13, 20-21, 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) the human PHEX enzyme of Figure 2 which has been modified such that selected amino acids in the signal peptide/transmembrane region have been substituted to increase PHEX solubility, and (2) an inactive mutant of the human PHEX enzyme of Figure 2 having a residue substitution at position 581 wherein said mutant has been modified to increase its solubility by amino acid substitutions in the signal peptide/transmembrane domain region, does not reasonably provide enablement for (1) any PHEX enzyme which has been modified in any way to increase its solubility, (2) any PHEX enzyme which has been modified in any way in the signal peptide/transmembrane region to increase its solubility, (3) any inactive PHEX enzyme which has been modified in any way to increase its solubility and is capable of binding any PHEX ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the large number of (1) unknown PHEX enzymes, (2) inactivating mutations in said enzymes which would not affect binding of any PHEX ligand, and (3) unknown modifications in the signal peptide/transmembrane region encompassed by the claims. As indicated above, the specification teaches a human PHEX enzyme in Figure 2 which has been modified at its transmembrane domain by substituting specific amino acids to increase its solubility. Furthermore, the specification teaches that a substitution of a glutamic acid residue for a valine residue at position 581 of the PHEX enzyme of Figure 2 would result in an inactive enzyme which still retains the ability to bind PHEX ligands. The specification however fails to disclose the structure of all the PHEX enzymes encompassed by the claims, the structural elements required to display PHEX activity, other methods to increase solubility of any PHEX enzyme, other modifications in the signal peptide/transmembrane region which would increase solubility, or other mutations in any PHEX enzyme which would inactivate the protein but would not alter the ability to bind any PHEX ligand.

While one could argue that the claimed invention is enabled since one can isolate PHEX enzymes by sequence comparison using the polypeptide structures disclosed in the instant application or the prior art, in combination with the teachings of the specification in regard to modifications which can increase their solubility, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches

that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Since structure determines function, one of skill in the art would require some knowledge or guidance as to how structure correlates with PHEX enzymatic function and its ability to bind ligands. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the structural elements required to display the desired function, and the unpredictability of the prior art in regard to determining function based on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate those polypeptides, as encompassed by the claim, and (2) practice the claimed method with such polypeptides. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1-2 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (Journal of Bone and Mineral Research 12(7):1009-1017, 1997; cited in previous Office Action Paper No. 8) in view of Lemire et al. (Biochem. J. 322:335-342, 1997; cited in the IDS). Guo et al. teaches the cloning of human PHEX (Figure 1, page 1013), formally known as PEX (phosphate regulating gene with homologies to endopeptidases on the X-chromosome; encoded by the XLH gene). Guo et al. teaches that PHEX has a high degree of homology with NEP, a neutral endopeptidase found in osteoblasts (page 1016, first column, second paragraph). Guo et al. does not teach a PHEX which has been modified at the transmembrane region for increased solubility. Lemire et al. teaches the expression and secretion of NEP soluble mutants in COS-1 cells (African green monkey kidney cells) including full length NEP mutants (page 338,

Expression of full-length NEP mutants in COS-1 cells). The NEP soluble mutants of Lemire et al. were obtained by introducing mutations in the signal peptide/transmembrane domain of NEP (Abstract, column 1, lines 1-9). The full length NEP mutants would include the ectodomain and the catalytic part. Lemire et al. does not teach soluble PHEX enzymes.

Claim 1 is drawn to a soluble PHEX enzyme and variant thereof, wherein the enzyme or the variant comprise the PHEX ectodomain or the catalytic domain. Claim 2 adds the limitation that the soluble PHEX enzyme and variant thereof have the signal peptide/transmembrane domain modified to increase solubility when expressed in a non-human eukaryotic host. Claim 13 is directed to an antigenic composition comprising the protein of claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify a human PHEX enzyme, as taught by Guo et al., to increase its solubility by mutating the signal peptide/transmembrane domain, as taught by Lemire et al. and express said soluble protein in a eukaryotic non-human host as taught by Lemire et al. The protein of Guo et al. and Lemire et al. would also be antigenic since any protein can be used to elicit antibodies. A person of ordinary skill in the art is motivated to obtain soluble human PHEX enzyme of Guo et al. and recombinantly express the soluble protein in a eukaryotic host cell such as COS-1 cells to (1) obtain large amounts of enzyme for further characterization since if it is recombinantly made, isolation from its natural source is no longer necessary, (2) make its purification easier since the protein if secreted can be recovered from the growth medium, and (3) obtain a protein which is post-translationally modified since prokaryotic hosts cannot perform post-translational modifications. One of ordinary skill in the art has a reasonable expectation of success at modifying the human PHEX enzyme of Guo et al. since Lemire et al. teaches how to obtain

soluble variants of a similar protein (NEP) by modifying the signal peptide/transmembrane region of NEP and expressing said variants in COS-1 cells. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

21. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (Journal of Bone and Mineral Research 12(7):1009-1017, 1997; cited in previous Office Action Paper No. 8) in view of Lemire et al. (Biochem. J. 322:335-342, 1997; cited in the IDS), as applied to claims 1 and 2 above, and further in view of Ni et al. (U.S. Patent No. 5840509, November 24, 1998). The teachings of Guo et al. and Lemire et al. have been discussed above. Neither Guo et al. nor Lemire et al. teach a method for obtaining a PHEX ligand. Ni et al. teaches an interleukin-1b converting enzyme (ICE) related protease (Abstract) and a method of finding agents which are functional ligands of the ICE protease (column 18, line 66, column 21, line 45) such as substrates (column 19, lines 45-52) or inhibitors (column 21, lines 5-45). Ni et al. does not teach a soluble PHEX enzyme.

Claim 33 is directed to a method of obtaining PHEX ligands by contacting a sample containing the test compounds with the soluble PHEX enzyme of claim 1, as described above, detecting binding between the ligand and the PHEX enzyme and selecting the ligand. Claim 34 adds the limitation that the ligand is a PHEX inhibitor or a substrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the soluble enzyme of Guo et al. and Lemire et al. in a method, as described by Ni et al., to obtain PHEX ligands which can be inhibitors or substrates. A person of ordinary

skill in the art is motivated to use the soluble human PHEX enzyme of Guo et al. and Lemire et al. in a method to obtain PHEX inhibitors or substrates to further characterize PHEX. One of ordinary skill in the art has a reasonable expectation of success at using the human soluble PHEX enzyme of Guo et al. and Lemire et al. since Ni et al. teaches a method for obtaining ligands of a ICE protease including substrates and inhibitors. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

22. No claim is in condition for allowance.

23. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

24. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
June 12, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1600